REMARKS

Claims 1, 2 and 6-8 are pending in the subject application. Claim 1 has been amended to more particularly point out what applicants regard as the invention. Applicants maintain that this amendment raises no issue of new matter. Applicants herein cancel claim 2 without prejudice. Accordingly, claims 1 and 6-8 will be pending and under examination in the subject application upon entry of this Amendment.

In view of the arguments set forth below, applicants maintain that the Examiner's rejections made in the May 27, 2005 Office Action have been overcome, and respectfully request that the Examiner reconsider and withdraw same.

Rejection under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 1, 2 and 6-8 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner asserts that references to "the nanomolar range" in claim 1 and "initially present at a concentration of 1-3 nanomolar" in claim 2 constitute new matter because the concept of each does not appear to be part of the originally filed invention.

In response to the rejection of claim 2, and without conceding the correctness thereof, applicants note that claim 2 has been canceled herein. Accordingly, the Examiner's rejection thereof is moot.

In response to the Examiner's rejection of claim 1 and dependent claims 6-8, applicants respectfully traverse. Applicants respectfully point out that claim 1, as amended, provides RNA in an amount between 1 and 3 nanomolar, and this range is supported by the specification at, *inter alia*, page 33, line 13 and page 38, lines 25-30.

In view of the above remarks, applicants respectfully request that the Examiner withdraw the rejection under 35 U.S.C. §112, first paragraph.

Rejections Under 35 U.S.C. §103(a)

The Examiner rejected claims 1, 2, 7 and 8 under 35 U.S.C. §103(a) as allegedly unpatentable over Shuman (1992) in view of Bjornson et al. (1994), as evidenced by Stern et al. (1998) and Karn et al. (2001).

In response to the Examiner's rejection of claim 2, and without conceding the correctness thereof, applicants note that claim 2 has been canceled herein. Accordingly, the Examiner's rejection thereof is moot.

In response to the Examiner's rejection of claims 1, 7 and 8, applicants respectfully traverse. Applicants maintain that the cited references fail to support a *prima facie* case of obviousness for the reasons of record and for the additional reasons set forth below.

According to M.P.E.P. §2143, to establish a *prima facie* case of obviousness, the Examiner must demonstrate three criteria with respect to each claim. First, as indicated above, the cited references, when combined, teach or suggest every

element of the claim. Second, one of ordinary skill would have been motivated to combine the teachings of the cited references at the time of the invention. And third, there would have been a reasonable expectation that the claimed invention would succeed.

Furthermore, to stress the above points, applicants direct the Examiner's attention to M.P.E.P §2143.03, which states that "[t]o establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

In light of these requirements, applicants assert that the cited references, taken together, fail to support a *prima facie* case of obviousness for claims 1, 7 and 8.

The instant claims provide a method for detecting the release of a single-stranded RNA from an RNA duplex. This method comprises the steps of (a) admixing an RNA helicase with the RNA duplex under conditions permitting the RNA helicase to unwind the RNA duplex and release single-stranded RNA therefrom, wherein the RNA duplex is (i) *present in an amount between 1 and 3 nanomolar* and (ii) comprises a first RNA having a first fluorescent label attached at its 5' end and a second RNA having a second label attached at its 3' end, wherein the first fluorescent label produces a luminescent energy pattern when the first RNA is present in the duplex, which differs from the luminescent energy pattern the first RNA produces when it is not present in the RNA duplex; and (b) detecting a change in the luminescent energy pattern produced by the first label so as to thereby detect release of single-stranded RNA from the RNA duplex.

Shuman teaches a method of detection by *gel electrophoresis* of RNA unwinding which uses a *radiolabel* attached to an RNA strand. Shuman fails to teach fluorescently labeled RNA or the detection of nanomolar amounts thereof.

Bjornson teaches a method for detecting the release of a single stranded *DNA* molecule from a *DNA* complex. Bjornson fails to teach fluorescently labeled RNA or the detection of nanomolar amounts thereof.

Stern describes in general terms a method utilizing fluorescently labeled RNA. Stern fails to teach the detection of nanomolar amounts of fluorescently labeled RNA. *See e.g.*, columns 14 and 15, and Figure 5 of Stern.

Karn describes in general terms the fluorescent labeling of an RNA on its 5' or 3' end. Karn does not teach a duplex RNA. Karn fails to teach the detection of nanomolar amounts of fluorescently labeled RNA. Instead, Karn uses labeled RNA to quench the fluorescent signal of a labeled antimicrobial compound. Thus, the labeled RNA is not detected in the method of Karn. Instead, the fluorescence of the labeled antimicrobial compound, and specifically the quenching of that fluorescence, is detected in the method of Karn. *See e.g.*, columns 20-24, and Figures 6-9.

According to M.P.E.P. §2141.02, the claimed invention must be considered *as a whole* when determining the differences between the prior art and the claims. In the present case, it is clear that the cited references in combination fail to teach each and every element of the claimed invention *as a whole* because certain elements are not taught by any of the references, e.g. a method using an RNA duplex present in an

amount between *1 and 3 nanomolar*. Shuman teaches detection of ssRNA between 20,000,000-50,000,000 nanomolar (Shuman at page 10937) which is greater than 1-3 nanomolar, while Bjornson teaches detection of nanomolar amounts of DNA only, *not* RNA (Bjornson at page 14310).

Contrary to the Examiner's position, the phrase "1 to 3 nonomolar", in relation to RNA, as recited in claim 1, is an element which must be taught by at least one reference. None of the cited references does this.

In response to applicants' previous arguments, the Examiner maintained that applicants have failed to address the combination of the references as a whole. In response, applicants maintain that reviewing each reference's teaching to show that none teaches this element is proper in the context of showing nonobviousness.

Furthermore, in response to applicants' previous arguments, the Examiner maintained that Shuman and Bjornson suggest that the fluorescent assay for detecting unwinding may be monitored using a concentration of nucleic acid as low as 1nM. In response, applicants again note that Shuman teaches the detection of 20,000,000-50,000,000nM of ssRNA substrate which, again, is greater than 1-3 nanomolar, while Bjornson teaches the detection of 1nM of DNA, *not RNA*. Therefore, one of ordinary skill in the art would not arrive at the subject invention by combining the teachings of the cited references, nor would she be motivated to try.

For the reasons above, the cited references combined fail to teach the elements of the claimed assay. Absent such teaching, there could not have been a motive to combine or a

reasonable expectation of success. Therefore, the cited references in combination fail to render obvious the claimed method.

The Examiner also rejected claim 6 under 35 U.S.C. §103(a) over Shuman in view of Bjornson further in view of Nazarenko (1999).

In response, applicants respectfully traverse for the reasons of record and the additional reasons set forth below.

Claim 6 depends from claim 1 and further provides that the first label is fluorescein isothiocyanate and the second label is rhodamine isothiocyanate.

According to the Examiner, Nazarenko teaches an extensive list of suitable moieties that can be used as donor or acceptor molecules for fluorescence resonance energy transfer ("FRET") reactions, including the fluorescein and rhodamine labels recited in claim 6. However, Nazarenko does nothing to overcome the deficiencies of Shuman or Bjornson in failing to teach the detection of nanomolar amounts of fluorescently labeled RNA. Specifically, Nazarenko fails to teach the element of using RNA duplex in an amount between *1 and 3 nanomolar*.

In response to applicants' previous arguments, the Examiner maintained that the combination of teachings of Shuman or Bjornson render obvious the detection of nanomolar amounts of fluorescently labeled RNA for the reasons of record. In response, applicants again direct the Examiner's attention to the remarks above regarding the failure of these references, when combined, to teach the elements of the rejected claims.

Therefore, Nazarenko combined with Shuman and Bjornson, fails to render obvious the claimed method.

The Examiner also rejected claims 1, 2, 7 and 8 under 35 U.S.C. §103(a) as allegedly unpatentable over Eggleston (1996).

In response to the rejection of claim 2, applicants again note that claim 2 has been canceled herein. Accordingly, the Examiner's rejection thereof is moot.

In response to the rejection of claims 1, 7 and 8, applicants respectfully traverse for the reasons of record and the additional reasons set forth below.

Eggleston teaches a helicase assay based upon dye displacement detection methods in which fluorescent dyes which bind to double-stranded *DNA* are displaced as the DNA is unwound. Eggelston teaches that "since this dye binds to RNA in addition to DNA, it is readily *conceivable* that RNA helicases *may* be amenable to this assay if an appropriate ligand...is utilized." (emphasis added). The Examiner states that Eggelston's teachings provide a reasonable expectation of success for practicing the claimed invention.

Applicants maintain that Eggleston fails to teach or suggest each and every element of the invention. Specifically, nowhere does Eggleston teach or suggest the element of using RNA duplex in the amount between *1 and 3 nanomolar*. Rather, Eggleston teaches an assay using *.01nM DNA* substrate which is not within 1-3 nanomolar. (Eggleston at page 1181). In addition, and without conceding the correctness of the Examiner's remarks, applicants stress that even if the dye of

Eggleston were reasonably expected to bind to RNA, one would not necessarily expect the claimed method to succeed absent applicants' own experimentation.

In response to applicants' previous arguments, the Examiner distinguishes between the 5'-end and the 5'-terminus regarding label attachment sites and maintains that applicants have failed to address this broad interpretation of the claims in any detail. In response, applicants assert that this issue need not be resolved in determining that the Eggleston reference, along with routine skill in the relevant art, fails to teach all limitations of the claims, i.e. Eggleston fails to teach an RNA duplex in an amount between 1 and 3 nanomolar.

In response to applicant's previous arguments, the Examiner maintained that the prior art teaches methods for attaching a luminescent dye to RNA. In response, applicants again maintain that, even assuming *arguendo* that Eggleston could motivate one to *try* the claimed invention, and that references exist which generally teach making RNA and attaching luminescent dye to RNA, these references alone would not present a reasonable expectation of success in doing so.

Accordingly, applicants maintain that Eggleston does not render the claimed invention obvious.

Finally, the Examiner rejected claims 1, 2, 7 and 8 under 35 U.S.C. §103(a) as allegedly unpatentable over Kowalczykowski et al. (1998).

In response to the rejection of claim 2, and without conceding the correctness thereof, applicants note that claim 2 has been

canceled herein. Accordingly, the Examiner's rejection thereof is moot.

In response to the rejection of claims 1, 7 and 8, applicants respectfully traverse for the reasons of record and the additional reasons set forth below.

Applicants maintain that Kowalczykowski, combined with routine skill, fails to teach or suggest each and every element of the invention. Specifically, applicants maintain that Kowalczykowski, along with routine skill in the relevant art, fails to teach the element of using RNA duplex in an amount between *1 and 3 nanomolar*. Rather, Kowalczykowski teaches an assay comprising *.01nM DNA* substrate. (Kowalczykowski at column 8, lines 63-67). Accordingly, Kowalczykowski, combined with routine skill, fails to teach all elements of the claims, and thus fails to render the claimed invention obvious.

In view of the above remarks, applicants maintain that the Examiner has failed to set forth a *prima facie* case of obviousness, and that accordingly, claims 1 and 6-8 satisfy the requirements of 35 U.S.C. §103(a).

Provisional Obviousness-Type Double Patenting Rejection

The Examiner provisionally rejected claims 1, 2 and 6-8 as allegedly unpatentable under the judicially created doctrine of obviousness-type double patenting over claims 1-8 of copending U.S. Application No. 10/182,362. According to the Examiner, a timely filed terminal disclaimer in compliance with 37 C.F.R. §1.321(c) may be used to overcome a provisional rejection based on a nonstatutory double patenting ground.

In response to the rejection of claim 2, and without conceding the correctness thereof, applicants note that claim 2 has been canceled herein. Accordingly, the Examiner's rejection thereof is moot.

In response to the rejection of claims 1 and 6-8, and without conceding the correctness of the Examiner's rejection, applicants will consider submitting a terminal disclaimer for claims 1 and 6-8 once the rejection is no longer provisional.

Summary

In view of the remarks made herein, applicants maintain that the claims pending in this application are in condition for allowance. Accordingly, allowance is respectfully requested.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

Respectfully submitted,

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